

URAD REPUBLIKE SLOVENIJE ZA INTELEKTUALNO LASTNINO

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(54) Naziv (*Title*):

Priprava amorfne pirolne spojine

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Ljubljana, 29.12.2004

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ZAHTEVA ZA PODELITEV PATENTA

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Datum vložitve prijave: 29 -12- 2003

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Priprava amorfnе pirolne spojine

6. Podatki o zahtevani prednostni pravici in podlagi zanjo:

7. Dodatne zahteve:


- ☐ prijava je za patent s skrajšanim trajanjem
- ☐ predhodna objava patenta po preteku _____ mesecev
- ☐ prijava je izločena iz prijave številka:

8. Izjava:

- ☐ izjava o skupnem predstavniku:

9. Priloge:

- ☒ opis izuma, ki ima 10 strani 2x
- ☒ patentni zahtevki (zahtevki), ki ima(jo) 3 strani; število zahtevkov: 13 2x
- ☒ skice (če so zaradi opisa izuma potrebne); število listov: 2
- ☒ povzetek 2x
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- ☐ generalno pooblastilo zastopniku je deponirano pri uradu pod št.: _____
- ☐ potrdilo o razstavni prednostni pravici
- ☐ podatki o drugih prijaviteljih
- ☐ podatki o drugih izumiteljih
- ☐ prikaz zaporedja nukleotidov ali aminokislin v opisu
- ☐ prijava je bila predhodno posredovana po faksu ali v elektronski obliki
- ☐

	
REPUBLIKA SLOVENIJA MINISTRSTVO ZA GOSPODARSTVO URAD RS ZA INTELEKTUALNO LASTNINO	
Prejeto dne: 29 -12- 2003	Osebnа oddaja: <input type="checkbox"/>
Podpis:	Oddano priporočeno dne:
Šifra:	Poštna številka: 23615

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Priimek in ime ter podpis prijavitelja (zastopnika)



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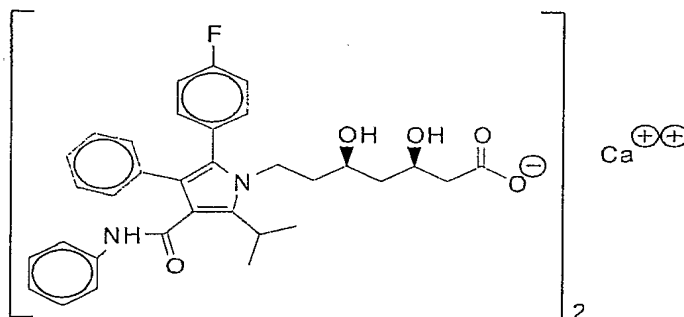
Preparation of amorphous pyrrole compound

Field of the invention

The invention relates to a process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester. This compound is useful pharmaceutical intermediate in the preparation of atorvastatin calcium.

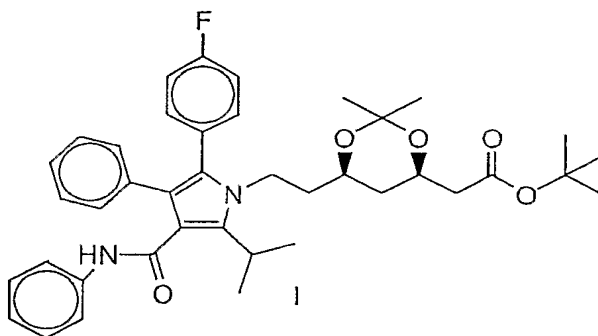
Technical background

Atorvastatin calcium, substance with the chemical name hemi calcium salt (R-(R*,R*))-(R)-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-((phenylamino)carbonyl)-1H-pyrrol-1-heptanoic acid and with the chemical formula



is an inhibitor of the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase). This enzyme is the catalyst of intracellular synthesis of cholesterol. HMG-CoA reductase inhibitors are useful for the treatment of dyslipidemia, hyperlipidemia, hypercholesterolemia, atherosclerosis, arteriosclerosis, cardiovascular disease, coronary artery disease, coronary heart disease, vascular disorder, inflammatory disease, allergic disease, neurodegenerative disease, malignant disease, viral disease, abnormal bone states, amyloid- β precursor protein processing disorders such as Alzheimer's disease or Down's Syndrome.

Substance (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester of the formula I



was first described in EP-B-330,172. The patent describes the preparation of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester.

Many different literature describes the preparation of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester and its further conversion into atorvastatin calcium as for example Tetrahedron Letters Vol.

33. Np. 17, 2283-2284 (1992), EP-A-553213, EP-A-643689, WO 02/043667, WO 02/059087, WO 02/083637, WO 02/083638, WO 03/016317, WO 03/082816.

WO 03/024959 relates to new crystalline forms I and II of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester and the process for the preparation thereof.

Recently a strong demand has arisen for pure and uniform products having physical properties appropriate for easily scaling-up procedure and using in industrial scale, as well. It is very important that compound (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester dissolves quickly and completely in aprotic solvents while the first step in the synthesis of atorvastatin calcium is dissolution of the said compound in an aprotic solvent. It is also desirable that the starting compound is pure and dry.

It is known from the literature that pure crystalline products are less soluble and that crystalline products are more difficult for purification in comparison to amorphous products. The reason for this is that usually larger crystal in the crystalline product incorporates larger amount of impurities during the crystal formation process while the amorphous products have very small particles in the solid formation process. Because of the smaller surface and specific area the amorphous product occludes and adsorbs smaller amount of impurities, residual solvents and residual gasses in comparison to the crystalline product. All the above mentioned objects are important from the economical point of view while when crystalline product is used the purification requires additional recrystallization step.

This invention provide the process for the preparation of pure amorphous material of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which can be easily used for the preparation of atorvastatin calcium. Amorphous starting compound in the sinthesys of atorvastatin calcium has an advantage in bettter solubility and in better purity.

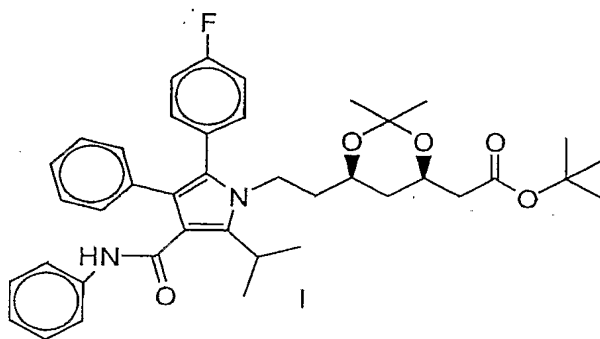
Description of drawings

Figure 1: An X-ray powder diffractogram of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester prepared by example 4.

Figure 2: DSC thermogram of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester prepared by example 2.

Detailed description of the invention

As mentioned before there exists a constant need for preparing amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrroll-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester of formula I



which is the key intermediate in the synthesis of preparing atorvastatin calcium. The main object of the present invention is therefore providing the process for the preparation of amorphous compound of the formula I that is used for the preparation of amorphous atorvastatin calcium. The developed process is simple and could be easily used for scaling-up and in industrial processes.

The first object of the invention is the process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid-tertiary butyl ester by dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester having undefined polymorph form in an organic solvent like methanol and concentrating the solution under vacuum until the solution is still absolutely clear. After that water is added to the solution to produce the precipitate of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid-tertiary butyl ester.

The second object of the invention is the process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid-

tertiary butyl ester by dissolving crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid-tertiary butyl ester in an inert organic solvent, selected from the group comprising methanol, acetonitrile, chloroform, methylene chloride, acetone, toluene and tetrahydrofurane, at room temperature or under heating. Amount of solvent should be high enough to produce completely clear solution. Then the solution is evaporated under reduced or normal pressure to completely remove the solvent out of the material. After that the residue is dried at room or increased temperature (up to 60°C) at normal or reduced pressure. The residue that is formed is amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester.

Regarding the solubility of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in comparison to the crystalline product the analyses show that the amorphous product is far better soluble in organic solvents as for example diisopropyl ether, isopropanol, methyl cyclohexane and lower alcohols.

The following nonlimiting examples illustrates the present invention without limiting the scope of invention to said Examples.

Example 1: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5g of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid -

tertiary butyl ester were dissolved in 100 ml of methanol. Clear solution was concentrated under vacuum to the point where the solution was still totally clear this means to the volume approximately 20 ml. Then 200 ml of water was added to form amorphous product. The precipitation was filtered out and dried under reduced pressure. The yield of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 4.46g.

Example 2: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5g of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 100 ml of acetonitrile. The clear solution was dried under vacuum until the completely dry product was obtained. The yield of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 5g.

Example 3: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5g of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 10 ml of methylene chloride. The clear

solution was dried under vacuum until the completely dry product was obtained. The yield of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 5g.

Example 4: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5g of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 5 ml of chloroform. The clear solution was allowed to stand without cover at room temperature for 5 hours or long enough to completely evaporate solvent out of the material. After that the residue was dried at 50°C under reduced pressure for 5 hours. The yield of the amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 5g.

Example 5: Preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

5g of (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester were dissolved in 5 ml of chloroform. The clear solution was dried under vacuum until the completely dry product was obtained. After that the residue was dried at 50°C under reduced pressure for 5 hours. The

yield of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester was 5g.

Example 6: X-ray powder diffraction analysis of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

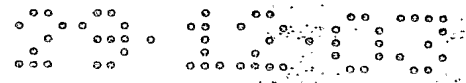
The amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester prepared by example 4 has an X-ray powder diffractogram substantially as shown in the Figure 1.

The X-ray powder diffraction pattern was collected on a Philips PW1710 diffractometer in reflection geometry. The instrument was regularly calibrated with a silicon standard. A standard Philips back-loading sample holder was used. Sample storage, mounting, and data collection were done at room temperature. Instrumental parameters were: CuK α radiation (30 mA, 40 kV, $\lambda = 1.5406 \text{ \AA}$, variable divergence slit (approx. $12 \times 16 \text{ mm}$ irradiated area), 0.4 mm receiving slit, graphite monochromator on the secondary side, scintillation counter. Data collection parameters were: 2θ range from 4° to 37° , step scan mode in steps of $0.04^\circ 2\theta$, integration time 1 second at each step.

Example 7: DSC analysis of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester

The DSC (Differential Scanning Calorimetry) analysis was performed on an Mettler Toledo DSC822e analyser. Measurement was performed in an unsealed Al pan with the heating rate of 5 K/min. The heating interval was 40-160°C. Thermogram of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester prepared by example 2 is expressed in the Figure 2.

The DSC curve shows the thermal transformation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester into crystalline forms. In the DSC curve we can clearly see the formation of crystals of Form II at around 120°C and melting point of these crystals at 136°C.



Claims

1. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an organic solvent and isolation of an amorphous product.
2. The process according to claim 1, wherein an organic solvent is methanol.
3. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises:
 - a) dissolving (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an organic solvent,
 - b) concentrating the solution,
 - c) adding water,
 - d) precipitation of the amorphous product.
4. The process according to claim 3, wherein an organic solvent is methanol.

5. The process according to claim 3, wherein the concentration of solution is performed under vacuum to the point where the solution is clear.
6. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises dissolving crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an inert organic solvent and isolation of an amorphous product.
7. The process according to claim 6, wherein an inert organic solvent is selected from the group consisting of methanol, acetonitrile, chloroform, methylene chloride, acetone, toluene or tetrahydrofuran.
8. A process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester, which comprises
 - a) dissolving crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester in an inert organic solvent,
 - b) isolation of the amorphous product.
9. The process according to claim 8, wherein the dissolving of crystalline (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic

acid - tertiary butyl ester in an inert organic solvent is performed at room temperature or under heating.

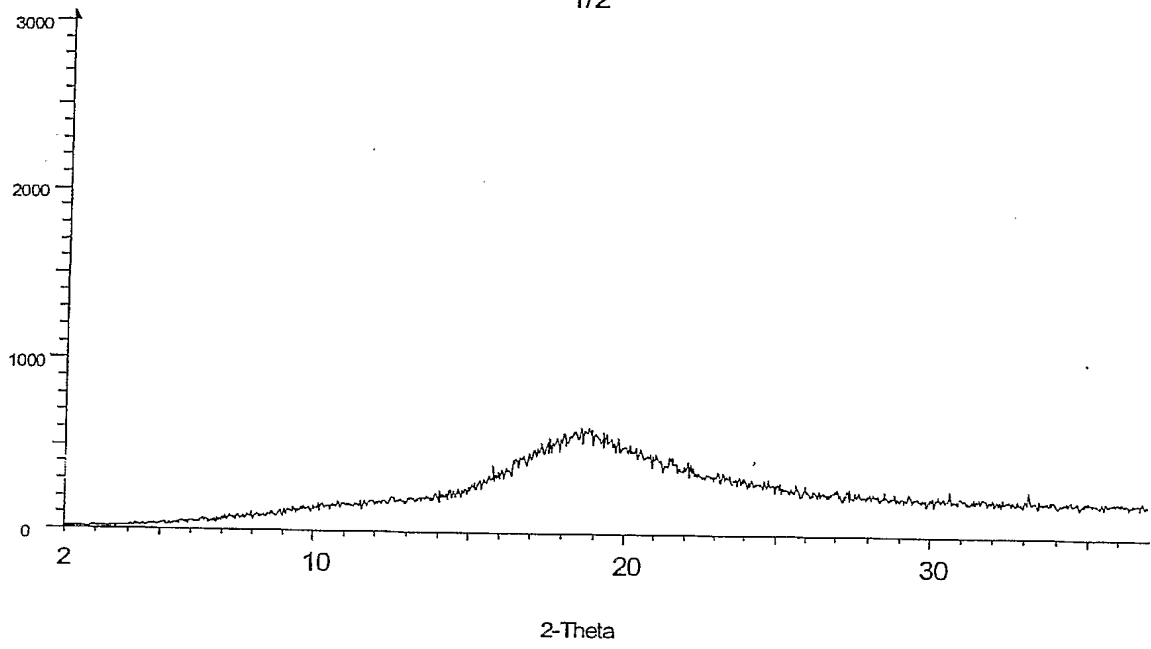
10. The process according to claim 8, wherein an inert organic solvent is selected from the group consisting of methanol, acetonitrile, chloroform, methylene chloride, acetone, toluene or tetrahydrofurane.
11. The process according to claim 8, wherein the isolation of the amorphous product comprises evaporating of the solvent at room or increased temperature at normal or reduced pressure.
12. Amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester having an X-ray powder diffractogram substantially as shown in the Figure 1.
13. Amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester having a DSC thermogram substantially as shown in the Figure 2.

Abstract

The invention relates to a process for the preparation of amorphous (4R-cis)-6-[2-[3-phenyl-4-(phenylcarbamoyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]-dioxane-4-yl-acetic acid - tertiary butyl ester which is useful pharmaceutical intermediate in the preparation of atorvastatin calcium.

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